Infection

Influenza virus associated encephalopathy

R Surtees, C DeSousa

Perspective on the paper by Hosoya *et al* (see page 469)

The neural complications of influenza are shown in box 1. The commonest of these, particularly in young children from Japan and Taiwan, is influenza virus associated encephalopathy. Influenza virus associated encephalopathy is an acute non-inflammatory encephalopathy that presents with seizures and coma on the day, or the day after, influenza symptoms start.[1] Influenza is characterised by the abrupt onset of a fever greater than 39°C, respiratory symptoms (rhinorrhoea, cough, and sore throat), myalgia (particularly of the back and limb muscles), and headache.[2] In infants symptoms are often lethargy, poor feeding, apnoea, and interstitial pneumonia; older children may also have less specific symptoms of croup, otitis media, diarrhoea, and vomiting.

INFLUENZA VIRUS ASSOCIATED ENCEPHALOPATHY

Influenza virus associated encephalopathy is a disease of young children with a peak incidence between 6 and 18 months of age.[1] It has mostly been reported from Japan and Taiwan, but cases have been reported from Europe and North America and in Caucasian children.[3] It is a severe disorder with a fatality of around 30%, and persisting neurodisability in around one third of survivors, associated with cerebral atrophy. The majority of cases complicate influenza A infections, but influenza B is responsible for around 10%.

Rapidly progressive neurological deterioration, seizures, and coma occur around 26 hours after the onset of influenza symptoms. Neuroimaging shows cerebral oedema in the majority of cases, but around 10–20% will show features of acute necrotising encephalopathy (see below). Death usually occurs within two days of the onset of neurological symptoms and in approximately half is caused by multi-organ failure.

The most severe form of influenza encephalopathy is acute necrotising encephalopathy. This is an acute, non-inflammatory encephalopathy in which symmetrical necrosis of the thalami and other deep brain structures, particularly the brain stem tegmentum, periventricular white matter, and cerebellar medulla, occurs. The necrosis may cause focal neurological signs and is evident on neuroimaging. Acute necrotising encephalopathy occurs in approximately one fifth of children with influenza encephalopathy. While influenza A is the most common cause of acute necrotising encephalopathy, it can complicate other respiratory tract infections in children (see box 2). Acute necrotising encephalopathy causes death or severe neurodisability in about 70% of affected children.

Influenza virus associated encephalopathy often has abnormalities of hepatic enzymes and/or function which may lead to the suspicion of Reye syndrome. However, Reye syndrome usually occurs during the recovery phase of influenza, is associated with the use of aspirin, is characterised biochemically by hyperammonaemia and hypoglycaemia, and has characteristic liver histopathology. None of these are found in influenza virus associated encephalopathy. The other differential diagnosis is influenza encephalitis which is suspected if the cerebrospinal fluid (CSF) shows pleiocytosis; in influenza virus associated encephalopathy there may be an increase in CSF protein (particularly with acute necrotising encephalopathy) but not an increase in leucocytes.

Investigators have consistently found raised concentrations of proinflammatory cytokines and their receptors (such as tumour necrosis factor α, interleukin-6, and soluble TNF-receptor 1) in plasma and CSF in children with influenza virus associated encephalopathy.[4–10] In addition, increased concentrations of the mitochondrial respiratory chain enzyme cytochrome *c* oxidase have also been found.[10] This suggests that apoptosis has occurred. When mitochondria undergo the permeability transition associated with inevitable cell death, cytochrome *c* oxidase is released into the cytoplasm where it triggers the execution phase of apoptosis by causing Apaf-1 mediated caspase activation. Excessive activation of caspases can also result in cell necrosis. These findings are likely to be important in our eventual understanding of the pathogenesis of influenza virus associated encephalopathy. Pathological examination of the brain in influenza virus associated encephalopathy suggests that direct viral invasion or inflammation are not involved in the pathogenesis, but that vascular inflammation has an important role as has apoptosis of the vascular endothelium and also the brain.[11 12] One set of hypotheses concerning the pathogenesis of influenza virus associated encephalopathy is: influenza infection in the genetically susceptible young child causes hypercytokinaemia; hypercytokinaemia causes vascular inflammation and endothelial apoptosis; lack of integrity of the cerebrovascular vessels allows seepage of plasma into the brain parenchyma; seepage of plasma causes cerebral oedema and triggers brain apoptosis (and necrosis in selectively vulnerable areas if the insult is severe enough).

PREDICTING THE DEVELOPMENT OF INFLUENZA VIRUS ASSOCIATED ENCEPHALOPATHY

Influenza virus associated encephalopathy is a biphasic disorder. For the first day the child has symptoms of influenza alone, and then the encephalopathy develops. Approximately one third of the children will die (half from multi-organ failure, half from brain stem failure), one third will survive with neurological sequelae and cerebral atrophy, and one third will recover. This is despite standard neurointensive care for a child with an acute encephalopathy

Box 1: Neural complications of influenza infection

- Encephalopathy
- Encephalitis
- Reye syndrome
- Febrile convulsion
- Myelitis
- Guillaine-Barré syndrome

Box 2: Causes of acute necrotising encephalopathy

- Influenza A and B
- Human herpes virus 6 and 7
- Herpes simplex virus
- Rubella
- Measles
- Varicella

which will include ventilation, circulatory support, treatment of seizures, monitoring and treatment of raised intracranial pressure, broad spectrum antibiotics, antivirals, and often immune modulators such as steroids.

If one could predict which children will develop severe influenza virus associated encephalopathy before the onset of encephalopathic symptoms, there is a chance that early or different treatment strategies might ameliorate the outcome. The former has been achieved by Hosoya and colleagues.[13] They measured plasma and serum concentrations of putative predictors (cytokines, cytochrome *c* oxidase, and markers of haematological, hepatic, and renal function) before and after the onset of the encephalopathic symptoms in children with influenza virus associated encephalopathy. They then examined the sensitivity, specificity, and cut-off concentrations of each putative predictor by constructing receiver operating characteristic (ROC) plots. Here, for each value of the putative predictor, the proportion predicting one outcome (the true positive rate (sensitivity); in this case death or neurological sequelae) is plotted against one minus the proportion predicting the alternative outcome (the true negative rate (specificity); in this case recovery). The area under the ROC curve is a measure of diagnostic accuracy and can be compared among the different putative predictors, the value at the upper left corner of the curve is the most discriminative cut-off level (giving the maximum likelihood ratio) and the sensitivity and specificity for this threshold level can be determined. Hosoya and colleagues found that pre-encephalopathy serum concentrations of cytochrome *c* oxidase had the greatest diagnostic accuracy, and the threshold value of 45 ng/ml or more predicted a poor outcome in influenza virus associated encephalopathy with a sensitivity of 93% and a specificity of 100%. This is clearly a very important finding, although, as the authors point out, it needs confirming.

The next question is whether being able to predict a poor outcome in influenza virus associated encephalopathy can lead to better treatment. That cytochrome *c* oxidase proves to be the most accurate predictor suggests that already the proposed pathogenic sequence is well underway and that endothelial apoptosis has occurred. It thus seems that severe influenza virus associated encephalopathy is inevitable. However, reduction of circulating cytokines (perhaps by plasma exchange or anti-cytokine antibodies) might limit the vascular damage and prevent the encephalopathy, procedures to prevent the cerebral oedema (such as fluid restriction, perhaps brain cooling, and thiopentone to reduce cerebral metabolism) might also be helpful and finally, acute endothelial repair might become possible using infusions of endothelial precursor cells.

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Authors' affiliations
R Surtees, UCL Institute of Child Health, London, UK
C DeSousa, Great Ormond Street Hospital for Children, London, UK

Correspondence to: Prof. R Surtees, The Wolfson Centre, Mecklenburgh Square, London WC1N 2AP, UK; R.Surtees@ich.ucl.ac.uk

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Diabetes

The great weight gain experiment, accelerators, and their implications for autoantibodies in diabetes

T J Wilkin

Perspective on the paper by Reinehr *et al* (see page 473)

Cause and effect can generally be established only by an intervention in which all extraneous variables are controlled. Usually, this means creating the artificial conditions of a randomised trial. Occasionally, the intervention comes about naturally.

For more than 50 years, mankind has been the subject of one such natural experiment—an intervention of unprecedented scale which has proved both a serious threat to health and an unexpected source of fundamental new understanding. The intervention has been that of extreme weight gain, amounting in adults to some 9 kg over the past generation.[1] The corresponding increase in children has been even greater.[2] The gains have not been in bone, muscle, or water, but in fat. Body fat—most particularly visceral fat—leads to insulin resistance, and insulin resistance to increasing demands on β-cell reserve.[3]

Diabetes is a disorder of β-cell failure in which insulin reserves are no longer sufficient to meet demand.[4] The rise of insulin resistance in contemporary society has served both to increase the incidence of diabetes and to accelerate its onset, so much so that type 2 diabetes, a disorder of middle age just